RISK MANAGEMENT PLAN

for

Vivlipeg® (pegfilgrastim)

Data lock point (DLP) for RMP: 20-Nov-2022

Version Number: 0.2

Dated: 11-Jun-2025

[redacted]

[redacted]

Risk Management Plan – Pegfilgrastim

Risk Management Plan for:	Pegfilgrastim
RMP Version number:	0.2
Data lock point for this RMP:	20-Nov-2022
Date of final sign-off:	11-Jun-2025
Rationale for submitting an updated RMP:	In response to Day 36 Rapporteurs joint assessment report for Vivlipeg.
Summary of significant changes in this RMP:	Part VI: Summary of the RMP (Section I. The medicine and what it is used for) was revised in line with the Guidance on the format of the risk management plan – Revision 2.0.1, as applicable to centrally authorised medicinal products. Annex 4: The content of the product-specific follow-up questionnaires for capillary leak syndrome and cytokine release syndrome was included in Annex 4 of the RMP. Annex 8: Updated with all the above-mentioned changes.
Other RMP versions under evaluation • RMP version number • Submitted on • Procedure number	Not applicable
Details of the currently approved RMP • Version number • Approved with procedure • Date of approval (Opinion date)	Not applicable; this is the initial RMP
QPPV name	Sanja Prpic
QPPV Signature	[redacted]
E-mail address of contact person	[redacted]

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List of abbreviations

Term/Abbreviation	Explanation
ADR	Adverse Drug Reaction
AERS	Adverse Event Reporting System
AKI	Acute Kidney Injury
ARDS	Acute Respiratory Distress Syndrome
ATC	Anatomical Therapeutic Chemical Classification System
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures – Human
CRS	Cytokine Release Syndrome
DDD	Daily Defined Dose
DLP	Data Lock Point
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
EURD	European Union Reference Date
G-CSF	Granulocyte-Colony Stimulating Factor
HCP	Healthcare Professional
HLT	MedDRA 'High Level Term'
ICSR	Individual Case Safety Report
IFN- γ	Interferon gamma
IL	Interleukin
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NK	Natural Killer (cells)
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	MedDRA 'Preferred Term'
PTY	Patient Treatment Years
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TGF	Transforming Growth Factor
TNF	Tumour Necrosis Factor
WHO	World Health Organization

Part I: Product(s) Overview

Table 1. Product overview

Active substance (s) (INN or common name):	Pegfilgrastim
Pharmacotherapeutic group (s): (Anatomical Therapeutic Chemical Classification System (ATC) Code):	Immunostimulants, colony-stimulating factor ATC Code: L03AA13
Marketing Authorisation Applicant:	Biosimilar Collaborations Ireland Limited
Medicinal products to which this RMP refers	1
Invented name (s)in the European Economic Area (EEA)	Vivlipeg 6 mg solution for injection in pre-filled syringe
Marketing authorisation procedure	Centralized procedure
Brief description of the product	Chemical class: Pegfilgrastim is a covalent conjugate of recombinant methionyl human G-CSF (r-metHuG-CSF) with a single 20 kd polyethylene glycol (PEG) molecule.
	Pegfilgrastim of Biosimilar Collaborations Ireland Limited (BCIL) - (trade name: Vivlipeg®) is a biosimilar medicinal product. Summary of mode of action: Filgrastim is produced by recombinant-DNA technology in E. coli. Pegfilgrastim and filgrastim belong to the class of haematopoietic growth factors (G-CSF). Pegfilgrastim is a sustained duration form of filgrastim due to decreased renal clearance. Pegfilgrastim and filgrastim have been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes. Similarly to filgrastim, neutrophils produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. As with other haematopoietic growth factors, G-CSF has shown in vitro stimulating properties on human endothelial cells. G-CSF can promote growth of myeloid cells, including malignant cells, in vitro and similar effects may be seen on some non-myeloid cells in vitro.
	Important information about its composition:

	Vivlipeg® pre-filled syringe contains 6 mg of pegfilgrastim* in 0.6 mL solution for injection. The concentration is 10 mg/mL based on protein only**. *Produced in Escherichia coli cells by recombinant DNA technology followed by conjugation with polyethylene glycol (PEG). ** The concentration is 20 mg/mL if the PEG moiety is included.
Hyperlink to the Product Information	Vivlipeg® Product information (Module 1.3.1)
Indication (s) in the EEA	Current: Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).
	Proposed: Not applicable.
Dosage in the EEA	Current: Pegfilgrastim therapy should be initiated and supervised by physicians experienced in oncology and/or haematology. Posology One 6 mg dose (a single pre-filled syringe) of pegfilgrastim is recommended for each chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy. Method of administration Vivlipeg® is injected subcutaneously. The injections should be given into the thigh, abdomen or upper arm. Paediatric population: The safety and efficacy of pegfilgrastim in children has not yet been established. Currently available data are described in Sections 4.8, 5.1 and 5.2 of the SmPC but no recommendation on a posology can be made. Patients with renal impairment: No dose change is recommended in patients with renal impairment, including those with end stage renal disease.
	Proposed: Not applicable.
Pharmaceutical form (s) and strengths	Current: Pre-filled syringes each containing 6 mg of pegfilgrastim in 0.6 ml solution for injection. The concentration is 10 mg/ml based on protein only. The concentration is 20 mg/ml if the PEG moiety is included.

	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes

Note: The proposed invented name, Vivlipeg is submitted by BCIL under a duplicate Marketing Authorisation Application (MAA) for the same pharmaceutical product; same qualitative and quantitative composition in active substance, forms, and strength as Fulphila – EMEA/H/C/004915.

Part II: Safety Specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable as this RMP pertains to a similar biologic. (Ref: In accordance with the Good Pharmacovigilance Practices (GVP) - Biological medicinal products[5].“All parts of an RMP are required for a biosimilar, except for RMP part II, module SI “Epidemiology of the target population).

Part II: Module SII - Non-clinical part of the safety specification

The non-clinical programme was designed to detect potential differences, and thereby establish similarity between Vivlipeg® and the reference biologics, Neulasta®. The programme was in accordance with relevant guidelines including European Medicines Agency (EMA) guidelines, “Guidance on Similar Medicinal Products containing Recombinant G-CSF, Annex To Guideline On Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Nonclinical and Clinical issues (EMEA/CHMP/BMWP/32775/2005)”, “ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals Step 5” (EMA/CHMP/ICH/731268/1998), and “Safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies are not routine requirements for non-clinical testing of similar biological medicinal products containing recombinant G-CSF as active substance (Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor: EMEA/CHMP/BMWP/31329/2005)”. The absence of secondary pharmacology studies and pharmacodynamic drug interaction studies is considered acceptable based on the extensive experience with and the well-known properties of filgrastim.

Table 2. SII.1 – Summary of Important Non-Clinical Safety Findings

Key Safety Findings (From Non-Clinical Studies)	Relevance to Human Usage
Repeat-Dose Toxicity	
One 2-way comparative repeat-dose (28-day) toxicity was conducted in rats. Vivlipeg® and the reference biologics (EU-sourced Neulasta®) were administered by subcutaneous route at doses of 0.15, 0.65, and 1.5 mg/kg of Vivlipeg® , or 0.15 and 1.5 mg/kg of Neulasta® once weekly for 4 consecutive weeks (5 doses total). Key results were as follows:	The results suggest similar toxicity (including similar local tolerance and low risk for immunogenicity) of Vivlipeg® and the reference biologics. Findings are adequately reflected in and minimized through product labelling.
• Expected and comparable treatment related increases in spleen weight and other pharmacodynamic markers were reported at 0.15 and 1.5 mg/kg body weight/day doses of Vivlipeg® , and EU-sourced Neulasta®.	Generally asymptomatic cases of splenomegaly and cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim. This risk is minimized through product labelling.
• Comparable profiles of toxicity at similar exposures were reported in rats dosed with Vivlipeg® or reference biologics.	In a post-marketing observational study conducted by the MAH of the reference biologics, pegfilgrastim in conjunction with chemotherapy and/or radiotherapy had been associated with development of myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) in breast and lung cancer patients. This risk is minimized

	through the product labelling and monitoring breast and lung cancer patients for signs and symptoms of MDS/AML.
• One moribund female rat in the high dose reference biologics group was sacrificed on day 28. Autopsy revealed granulocytic leukaemia lesions (widespread diffuse invasive proliferation of myeloid cells) in spleen, bone marrow and multiple organs including non-haemopoietic tissues). • Clinical chemistry: Elevated and comparable alkaline phosphatase and aspartate aminotransferase levels were reported in male and female rats dosed with equal amounts of either Vivlipeg® or reference biologics. These increases did not correspond to any remarkable hepatotoxicity as determined by pathology. In the liver, increased haemopoiesis (predominantly myeloid cells in periportal areas) was recorded with 1.5 mg/kg/day Vivlipeg® or Neulasta® • Expected and comparable increases in haematopoiesis (increases in leukocytes) were reported in rats dosed with Vivlipeg® or reference biologics. Preclinical data from conventional studies of repeated dose toxicity with reference biologics revealed the expected pharmacological effects including increases in leukocyte count, myeloid hyperplasia in bone marrow, extramedullary haematopoiesis and splenic enlargement.	White blood cell (WBC) counts of 100 × 109/L or greater have been observed in less than 1 % of patients receiving pegfilgrastim. No adverse events directly attributable to this degree of leukocytosis have been reported. Such elevation in white blood cells is transient, typically seen 24 to 48 hours after administration and is consistent with the pharmacodynamic effects of this medicinal product. This risk is minimized through the product labelling.
<u>Immunogenicity</u>: Based on toxicokinetic data demonstrating the expected exposure, the absence of any anaphylactic reactions, and the expected increases in pharmacodynamic markers, and due to the species difference the immunogenicity of Viatris's (ex-MAH) human pegfilgrastim was not evaluated in rats following the above repeat-dose toxicity study. <u>Local tolerance</u>:	As with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against pegfilgrastim is generally low. This risk is minimized through product labelling. No particular risk to humans is inferred

In the repeat-dose toxicity study, no local reactions were observed at the injection site of Vivlipeg® in either male or female rats. No evidence of local intolerance was observed during a single dose pharmacodynamic study in rats. Histopathology performed on tissues collected at the injection sites during the repeat-dose toxicity study identified minimal fasciitis/fibrosis and occasional haemorrhage but these observations occurred with similar frequency and severity in rats dosed with equal amounts of Vivlipeg® or the reference biologics.	
Reproductive and Developmental Toxicity Reproductive and developmental toxicity studies have not been performed with Vivlipeg® . Preclinical studies with reference biologics did not reveal adverse effects in offspring from pregnant rats given pegfilgrastim subcutaneously, but in rabbits pegfilgrastim has been shown to cause embryo/foetal toxicity (embryo loss) at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose. In rat studies, it was shown that pegfilgrastim may cross the placenta. Studies in rats indicated that reproductive performance, fertility, oestrous cycling, days between pairing and coitus, and intrauterine survival were unaffected by pegfilgrastim given subcutaneously	Data from the post-market setting did not reveal any patterns suggestive of a safety concern and did not indicate any safety signals with the use of pegfilgrastim during pregnancy or lactation.
Genotoxicity No genotoxicity studies have been undertaken with Vivlipeg® . This is acceptable given the biotechnological origin of the product. In an Ames assay performed by the innovator filgrastim was not mutagenic	No particular risk to humans is inferred.
Carcinogenicity No carcinogenicity studies have been undertaken with Vivlipeg®. A 6-month carcinogenicity study with Neulasta® was conducted by the innovator in Sprague Dawley rats injected once-weekly with doses up to 1000 µg/kg subcutaneously. The results from the study did not identify any precancerous or cancerous lesions.	No particular risk to humans is inferred based on both animal studies as well as reassuring clinical data on filgrastim and pegfilgrastim.

Other Toxicity-Related Information or Data In animal models, concomitant administration of reference biologics and 5-fluorouracil or other antimetabolites has been shown to potentiate myelosuppression.	Specific interaction or metabolism studies have not been performed in humans, however, clinical trials have not indicated an interaction of the reference biologics with any other medicinal products. No additional risks to humans are inferred.

Results from the non-clinical testing program demonstrate that Vivlipeg® formulation was biologically equivalent to the reference biologics .

Part II: Module SIII - Clinical Trial Exposure

Vivlipeg® is another proposed invented name for pegfilgrastim in the EMA region. Pegfilgrastim is also already approved and marketed under the trade name of Fulphila®.

Vivlipeg® has been developed as a similar biological medicinal product for reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes). Mylan (Ex-MAH) has sponsored the following three clinical trials to establish similarity with the reference medicinal product, Neulasta® in terms of pharmacokinetics, pharmacodynamics, safety and efficacy:

- MYL-1401H-1001: A Phase 1 single centre, randomised, double-blind crossover study conducted in 216 healthy subjects to compare pharmacokinetics, pharmacodynamics, safety and tolerability of MYL-1401H compared to reference biologics EU- and US-sourced Neulasta®.
- MYL-1401H-1002: A Phase 1 single centre, randomised, open-label, 2-dose, parallel study conducted in 50 healthy subjects to descriptively compare immunogenicity between 2 SC injections of MYL-1401H and US-sourced Neulasta® and to evaluate the safety and tolerability of MYL-1401H and US-sourced Neulasta®.
- MYL-1401H-3001: A Phase 3 multicentre, randomised, double-blind therapeutic equivalence study conducted in 194 adult patients with Stage II/III invasive breast cancer in the adjuvant/neo-adjuvant setting receiving chemotherapy with docetaxel, doxorubicin, and cyclophosphamide to compare the efficacy, safety, and immunogenicity of MYL-1401H and EU-sourced Neulasta®.
- PEGF-IJZ-1003: A Phase 1 randomized, blinded, 2-period, 2 treatments, 2-way crossover trial to assess pharmacokinetics (PK) / pharmacodynamics (PD), safety and tolerability of MYL-1401H after single subcutaneous injection at one dose level (3.6 mg) compared to G-Lasta® in healthy adult Japanese volunteers.

The following tables summarise clinical trial exposure to MYL-1401H (Vivlipeg®). The three Phase 1 studies (MYL-1401H- 1001, MYL-1401H-1002 and PEGF-IJZ-1003) were conducted in healthy volunteers. The Phase 3 trial MYL- 1401H-3001 was conducted in adult patients with invasive breast cancer.

Due to the diverse study populations (healthy volunteers and patients, respectively), data have not been pooled across clinical trials and clinical trial exposure by dose and duration, age, gender and ethnicity is therefore summarised separately per study in the following tables. All numbers refer to the number of patients who received at least one dose of MYL-1401H (Vivlipeg®) (safety population). In studies MYL-1401H-1001 and MYL-1401H- 3001, patients were randomised to receive either MYL-1401H (Vivlipeg®) or a reference biologics; the following tables do not include patients who received reference product only. In studies MYL-1401H-1002 and PEGF-IJZ-1003, study subjects also received reference biologics .

Table 3. SIII.1 – Clinical Trial Exposure to MYL-1401H (Vivlipeg®) by Dose*

Study ID	Study Population	Dose	Number of Subjects Exposed
MYL-1401H-1001	Healthy adult subjects	1 × 2 mg SC	207
MYL-1401H-1002	Healthy adult subjects	1 - 2 × 6 mg SC	25
MYL-1401H-3001	Patients with invasive breast cancer	6 × 6 mg SC	127
PEGF-IJZ-1003	Healthy adult subjects	1 x 3.6 mg	169
Total number of subjects exposed to MYL-1401H (Vivlipeg®)			**528**

* Table displays number of subjects who received at least one dose of MYL-1401H (Vivlipeg®) (safety population). Studies MYL-1401H-1001 and MYL-1401H-3001 also included patients who received reference biologics only; these patients are not counted. In MYL-1401H-1002, and PEGF-IJZ-1003 studies, patients who received PEGF-IJZ (Vivlipeg®) also received reference biologics. Unblinded exposure data from study PEGF-IJZ-1003 had become available after the DLP, nevertheless they have been included.

Table 4. SIII.2 – Clinical Trial Exposure to MYL-1401H (Vivlipeg®) by Age

Study ID	Mean Age and Age Range	Number of Subjects Exposed
MYL-1401H-1001	Mean ± SD: 37 ± 14; range 18-65 years*	207
MYL-1401H-1002	Mean ± SD: 35 ± 15; range 19-65 years	25
MYL-1401H-3001	Mean ± SD: 50 ± 11; range 25-79 years >65 years: 7 (5.5%)	127
PEGF-IJZ-1003	Mean ± SD: 34 ± 9; range: 20-55 years	169
Total number of subjects exposed to MYL-1401H (Vivlipeg®)		**528**

* These statistics include the entire safety population of study MYL-1401H-1001 (N=216), including 9 patients who received reference biologics but not Vivlipeg ®

Table 5. SIII.3 – Clinical Trial Exposure MYL-1401H (Vivlipeg®) by Gender

Study ID	Male	Female	Total
MYL-1401H-1001	170*	46*	207
MYL-1401H-1002	13	12	25
MYL-1401H-3001	1	126	127
PEGF-IJZ-1003	169	0	169
Total	**358***	**184***	**528**

* These statistics include the entire safety population of study MYL-1401H-1001 (n=216), including 9 patients who received reference biologics but not Vivlipeg®

Table 6. SIII.4 – Clinical Trial Exposure to MYL-1401H (Vivlipeg®) by Ethnic Origin

Racial Group	MYL-1401H-1001	MYL-1401H-1002	MYL-1401H-3001	PEGF-IJZ-1003	Total
White	196*	20	127	0	343*
Black or African American	6*	1	0	0	7*
Asian	5*	1	0	169	175

American Indian or Alaska Native	2*	0	0	0	2*
Other	7*	3	0	0	10*
Total	**207***	**25**	**127**	**169**	**528**

* These statistics include the entire safety population of study MYL-1401H-1001 (n=216), including 9 patients who received reference biologics but not Vivlipeg®

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Many exclusion criteria applied in the clinical development programme aimed for optimization of study conduct and minimization of bias and confounding of study results, and are unrelated to safety concerns (e.g., present or past significant medical or psychiatric comorbidity, substance abuse, etc.). These exclusion criteria thus need not be addressed in the labelling of the marketed product.

Exclusion criteria relating to known or suspected safety concerns (e.g., history of hypersensitivity to the study medications or to other *E. coli*-derived products, sickle cell disorders, splenomegaly of unknown origin, myeloproliferative or myelodysplastic disorders, pulmonary disease, elevated liver function tests or treatment with lithium; see Section SVII) have been carried forward as contraindications or warnings in the Summary of Product Characteristics proposed for the marketed product.

Some clinical trial exclusion criteria aimed to protect potentially vulnerable populations (e.g., women not using effective birth control methods, pregnant or breastfeeding women, and children). The clinical implications of the resultant limitations to the clinical trial results are discussed in the following section.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 7. SIV - Exposure of special populations included or not in clinical trial development programmes

Type of Special Population	Exposure
Paediatric population	Not included in the clinical development program
Elderly patients	Clinical trial experience with Vivlipeg® includes only a few older patients (>65 years)
Pregnant Women	Not included in the clinical development program
Breastfeeding Women	
Population with Relevant Different Ethnic Origin	Not included in the clinical development program>

Patients with Hepatic Impairment or Renal Impairment	Not included in the clinical development program
Patients with Other Relevant Co-Morbidity	Not included in the clinical development program
Patients with a disease Severity Different from the Inclusion Criteria in the Clinical Trial Population	Not included in the clinical development program
Subpopulations Carrying Relevant Genetic Polymorphisms	Not included in the clinical development program
Patients of Different Racial and/or Ethnic Origin	All patients enrolled in the Phase 3 clinical trial with Vivlipeg® were Caucasian.

Part II: Module SV - Post-authorisation Experience

SV.1 Post-authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Vivlipeg® is another proposed invented name for pegfilgrastim in the EMA region. Pegfilgrastim is also already approved and marketed under the trade name of Fulphila®.

The MAH is marketing pegfilgrastim in Austria, Bangladesh, Brazil, Canada, Colombia, Croatia, Czech Republic, Finland, France, Germany, Greece, Guatemala, Hungary, Israel, Italy, Malaysia, Pakistan, Singapore, Slovakia, South Africa, Sweden, Switzerland, Taiwan, Thailand, the United Arab Emirates and the United States of America. The patient exposure has been estimated based on the available cumulative sales data for pegfilgrastim. This data is gathered worldwide from Viatris Inc (ex-MAH). These figures are compiled from data available at the time of writing and may not represent exact patient consumption. They may include packs that are lodged with wholesalers, pharmacists or representatives.

The calculations for pegfilgrastim have been done based on the WHO Defined Daily Dose (DDD) for pegfilgrastim, which is 0.3 mg.

The methodology used for calculating an estimate of patient exposure for pegfilgrastim is:

$$\text{Patient Treatment Years (PTY)} = \frac{\text{Total mg sold}}{\text{WHO DDD} \times 365}$$

SV.1.2 Exposure

The patient exposure has been presented below from the date of the initial sale until the data lock point of this report.

Table 8. SV - Cumulative exposure from non-study post-authorisation exposure by dose and country*

Formulation	Country	Strength	Batch Number (for biologics)	Quantity Sold	Total Mg Sold	Exposure in PTY
Solution for injection in prefilled syringes	Austria	6mg/0.6ml	BF19006726 BF20004003 BF20005255 BF20005741	1,904	11,424	104

Solution for injection in prefilled syringes	Bangladesh	6mg/0.6ml	BF20005687 BF21002861 BF21004782 BF22001923	1,050	6,300	58
Solution for injection in prefilled syringes	Brazil	6mg/0.6ml	BF21000620 BF21000706 BF21005522	1,945	11,670	107
Solution for injection in prefilled syringes	Canada	6mg/0.6ml	BF20002624 BF20001217 BF20002725 BF20002625 BF20001216 BF19000413 BF19006716	8,683	52,098	476
Solution for injection in prefilled syringes	Colombia	6mg/0.6ml	BF21001146 BF21001177 BF21001901 BF21005523 BF22000177	9,250	55,500	507
Solution for injection in prefilled syringes	Croatia	6mg/0.6ml	BF20001059 BF20002237 BF20002711 BF21001546	2,208	13,248	121
Solution for injection in prefilled syringes	Czech Republic	6mg/0.6ml	BF19006892 BF20000785 BF20002486	1,422	8.532	78
Solution for injection in prefilled syringes	Finland	6mg/0.6ml	BF19006891 BF20001135 BF20002488 BF21003305	4,753	28,518	260
Solution for injection in			BF19006568 BF20000036 BF20000228 BF20000428 BF20000454 BF20000701 BF20001058 BF20001158 BF20001253 BF20002489 BF20002715 BF20003986 BF20004365 BF20005137 BF20005291 BF21000162			

prefilled syringes	France	6mg/0.6ml	BF21001383 BF21001547 BF21001729 BF21003463 BF21003464 BF21005439 BF21005440	54,495	326,970	2,986
Solution for injection in prefilled syringes	Germany	6mg/0.6ml	BF19006726 BF20001057 BF20002236 BF20002487 BF20004001 BF20004812 BF20005255 BF20005365 BF20005741	19,227	115,362	1,053
Solution for injection in prefilled syringes	Greece	6mg/0.6ml	BF20002709 BF20002710 BF20004364 BF20005197 BF20005643 BF21003462 BF21003465	13,996	83,976	767
Solution for injection in prefilled syringes	Guatemala	6mg/0.6ml	BF20003513	1,421	8,526	78
Solution for injection in prefilled syringes	Hungary	6mg/0.6ml	BF20001018 BF20004002	249	1,494	14
Solution for injection in prefilled syringes	Israel	6mg/0.6ml	BF20004172 BF20004173 BF20005644 BF21001341 BF21001903 BF21001948 BF21002552 BF21003700 BF21005259 BF21005260 BF21005261 BF22000321	29,843	179,058	1,635
Solution for injection in prefilled syringes	Italy	6mg/0.6ml	BF21002585 BF21005246	3,966	23,796	217

Solution for injection in prefilled syringes	Malaysia	6mg/0.6ml	BF21003461 BF20003446 BF20001920	1,719	10,314	94
Solution for injection in prefilled syringes	Pakistan	6mg/0.6ml	BF21004189 BF21004895 BF22000179	3,000	18,000	164
Solution for injection in prefilled syringes	Singapore	6mg/0.6ml	BF21003443 BF21003682 BF22000860 BF22002813 BF22003333 BF22003478	12,979	77,874	711
Solution for injection in prefilled syringes	Slovakia (Slovak Republic)	6mg/0.6ml	BF20000703 BF20002486 BF20002713 BF21000162 BF21003651	4,183	25,098	43
Solution for injection in prefilled syringes	South Africa**	6mg/0.6ml	NA	0	0	0
Solution for injection in prefilled syringes	Sweden	6mg/0.6ml	BF19006725 BF20001135 BF20002488 BF21003305	784	4,704	43
Solution for injection in prefilled syringes	Switzerland	6mg/0.6ml	BF20000886 BF20002712 BF20005642 BF20005195 BF21001545	223	1,338	43
Solution for injection in prefilled syringes	Taiwan	6mg/0.6ml	BF20001462 BF20005719 BF22000098	1,183	7,098	65
Solution for injection in prefilled syringes	Thailand	6mg/0.6ml	BF18005301 BF20001463 BF20001919 BF20003446 BF20001920	2,053	12,318	112

Solution for injection in prefilled syringes	United Arab Emirates	6mg/0.6ml	BF21001157 BF21004763 BF22005696	1,498	8,988	82
Solution for injection in prefilled syringes	United States of America	6mg/0.6ml	BF18001472 BF18001473 BF18001474 BF18001475 BF18001476 BF18001477 BF18001478 BF18001479 BF18001480 BF18001607 BF18001608 BF18001930 BF18001931 BF18002163 BF18002164 BF18003031 BF18003032 BF18003074 BF18003103 BF18003104 BF18003105 BF18003828 BF18003829 BF18003860 BF18003963 BF18004470 BF18004471 BF18004472 BF18005201 BF18005202 BF18005246 BF18005823 BF18006740 BF18006741 BF18006866 BF18006947 BF18007558 BF19000153 BF19000155 BF19000156 BF19000439 BF19000606 BF19000607 BF19000608 BF19000609 BF19000667 BF19001168 BF19001169 BF19001218 BF19001219 BF19001220	441,717	2,650,302	24,204

			BF19001239 BF19001240 BF19001241 BF19001277 BF19001278 BF19001279 BF19001939 BF19002015 BF19002478 BF19002663 BF19002664 BF19002665 BF19002687 BF19002688 BF19002689 BF19003091 BF19003151 BF19003241 BF19003274 BF19003275 BF19003312 BF19003313 BF19003712 BF19003944 BF19003945 BF19003972 BF19004418 BF19004419 BF19004420 BF19004421 BF19004422 BF19004423 BF19004424 BF19004425 BF19004426 BF19004427 BF19004428 BF19004581 BF19004941 BF19004942 BF19005002 BF19005160 BF19005219 BF19005261 BF19005484 BF19005594 BF19006576 BF19006577 BF19006578 BF19006579 BF19006787 BF19006788 BF19006789 BF19007077 BF20000171 BF20001092			

			BF20001107 BF20001108 BF20001109 BF20002744 BF20002745 BF20002746 BF20003515 BF20004448 BF20004449 BF20004473 BF20004497 BF20004518 BF20004558 BF20004577 BF20004704 BF20005301 BF20005302 BF20005303 BF20005708 BF20005720 BF21000023 BF21000024 BF21000717 BF21000718 BF21001336 BF21002013 BF21002014 BF21002015 BF21002157 BF21002158 BF21002159 BF21002210 BF21002211 BF21002212 BF21003203 BF21004446 BF21004447 BF21004448 BF21004720 BF21004721 BF21004760 BF21004761 BF21005021 BF21005070 BF21005071 BF21005106 BF21005107 BF21005108 BF22000079 BF22000080 BF22001141			
Total				**623,751**	**3,742,506**	**34,178**

*Sales data of business partner Biocon were not included

**Pegfilgrastim was launched in South Africa in Dec-2022 only, therefor no sales data were presented

The total worldwide exposure to pegfilgrastim since first market launch is estimated to be 34,178 patient treatment years (PTY).

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

The product is restricted by prescription only. This is not a substance abuse drug and there is no potential for misuse of pegfilgrastim for illegal purposes.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

On 22-Aug-2022, the product Neulasta® was authorised by the European Commission according to EMA product number- EMEA/H/C/000420. Accordingly, the safety concerns for Vivlipeg® are based on the list of safety concerns as presented in the European Public Assessment Report (EPAR) for Neulasta® (date 23-Oct-2023) [1]

Table 9. SVII.1 - Summary of safety concerns

Summary of safety concerns	
Important Identified Risks	• Capillary leak syndrome • Acute respiratory distress syndrome • Sickle cell crisis in patients with sickle cell disease • Glomerulonephritis
Important Potential Risks	• Cytokine release syndrome
Missing Information	• None

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable, as all risks from reference biologics RMP have been considered in this RMP.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

All safety concerns in the RMP for the biosimilar product Vivlipeg® are solely based on the safety concerns for the reference biologics Neulasta® (Amgen Europe B.V.) containing Pegfilgrastim. Same are listed under SVII.1.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable as this is the initial RMP for Vivlipeg®.

[redacted]

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

All the risks and missing information presented here are in line with reference biologics Neulasta® RMP, dated 23 Oct 2023.

Important Identified Risks	• Capillary leak syndrome • Acute respiratory distress syndrome • Sickle cell crisis in patients with sickle cell disease • Glomerulonephritis
Important Potential Risks	• Cytokine release syndrome
Missing Information	• None

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Table 10. SVII.2 - Important Identified Risk: Capillary leak syndrome

Potential Mechanisms	Capillary leak syndrome is characterized by an increased capillary permeability to proteins leading to an escape of plasma from the blood circulatory system to surrounding tissues. Capillary leak syndrome can be idiopathic or secondary to autoimmune diseases, malignant hematological diseases, viral infections, snakebites, and treatment with some antineoplastic and immunomodulating agents. **(Amoura ZMD,1997)** [1] and **(Izzedine H,2022)** [2]. The mechanism by which G-CSF can cause capillary leak syndrome is not known. Several hypotheses have been proposed, including a direct endothelial effect of G- CSF **(Park KW, 2008)** [3] or endothelial damage caused by superoxide anion radicals produced by the activated and increased granulocytes. **(Oeda E, 1994)** [4]
Evidence Source(s) and Strength of Evidence	Based on the published literature data and in line with the RMP for the reference biologics , this safety concern has been classified as an important identified risk
Characterisation of the Risk	Frequency in Viatris's (ex-MAH) clinical trials: Capillary leak syndrome was not reported as an adverse event from the clinical trials with Vivlipeg®. Frequency with reference product: The SmPC of the reference product lists capillary leak syndrome as an uncommon undesirable effect. Background incidence/prevalence: Capillary leak syndrome is a rare disease, with only isolated case reports having been reported worldwide. Mean age of onset is 45 years; paediatric or geriatric cases are rare. **(Amoura Z, 2012)** [5] Seriousness/outcomes: Capillary leak syndrome is a potentially life-threatening condition if treatment is delayed, regardless of its cause. A

	mortality rate of 30-40% has been reported. **(Amoura Z, 2012)** [5] Severity and nature of risk: Capillary leak syndrome is a potentially severe condition characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration. Severity ranges from mild hypotension responding to oral hydration to very severe clinical courses with rhabdomyolysis, renal failure and acute pulmonary oedema that may be fatal, especially if treatment is delayed **(Amoura Z, 2012)** [5]. Cases associated with filgrastim mostly occurred after the first dose. **(MHRA, 2014)** [6] Impact on individual patient: The impact on individual patient will depend on the clinical course. Post-marketing data Cumulatively up to the DLP of this RMP, the company has not received any cases for pegfilgrastim reporting events pertaining to MedDRA PT 'Capillary leak syndrome'.
Risk Factors and Risk Groups	The cases of capillary leak syndrome reported in association with the reference product have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis. **(MHRA, 2014)** [6]
Preventability	Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care
Impact on the Risk-Benefit Balance of the Product	The risk associated with the use of pegfilgrastim is minimized through provision of relevant product information to support safe use of the product
Public Health Impact	As the incidence of severe capillary leak syndrome to pegfilgrastim seems to be low, the public health impact of this safety concern is considered to be low despite its potentially severe clinical course

Table 11. SVII.3 - Important Identified Risk: Acute respiratory distress syndrome

Potential Mechanisms	It has been postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs **(Amgen Canada Inc, 2021)** [7]
Evidence Source(s) and Strength of Evidence	Based on the published literature data and in line with the RMP for the reference product, this safety concern has been classified as an important identified risk
Characterisation of the Risk	Frequency in Viatris's (ex-MAH) clinical trials: No events of acute respiratory distress syndrome (ARDS), interstitial pneumonia or other relevant pulmonary reactions

	were reported from the clinical trials with Vivlipeg® . Frequency with reference product: The SmPC of the reference product lists pulmonary reactions including interstitial pneumonia, pulmonary oedema, pulmonary infiltrates, pulmonary fibrosis and ARDS as uncommon undesirable effects, indicating for ARDS that it was identified through post-marketing surveillance but not observed in randomised, controlled clinical trials in adults and that the frequency category was estimated from a statistical calculation based upon 1,576 patients receiving Neulasta® in clinical trials. Background incidence/prevalence: Pulmonary disease in general is common and may have numerous causes. Incidence and prevalence vary strongly depending on the specific nature of the event, observed populations, and causative agents, thereby impeding presentation of meaningful figures. For example, the incidence of ARDS has been reported to be approximately 70 cases/100,000 person-years in the US, 34/100,000 in Australia and New Zealand, 17/100,000 in Northern Europe and 7/100,000 in Spain **(Walkey AJ, 2012)** [8]**.** Seriousness/outcomes: Pulmonary adverse events such as interstitial pneumonia and ARDS are potentially life-threatening conditions. For example, ARDS is associated with a hospital mortality of approximately 40% and many patients with ARDS develop long-term symptoms or require long-term health services after hospital discharge. **(Walkey AJ, 2012)** [8] Severity and nature of risk: Clinically severe events such as interstitial pneumonia, pulmonary oedema, pulmonary infiltrates, pulmonary fibrosis and ARDS have been reported in association with the reference product. As G-CSF was given in combination with cytotoxic drugs known to induce pulmonary toxicity in most published cases, some authors have suggested that G-CSF therapy does not contribute significantly to the pulmonary disease. **(Azoulay E, 2001)** [9] Impact on individual patient: The impact on individual patient will depend on the specific nature of the pulmonary event and its clinical course. Post-marketing data The search restricted to MedDRA PT 'acute respiratory distress syndrome' has not identified any cases for pegfilgrastim relevant for this safety concern in the company safety database cumulatively up to the DLP of this RMP.
Risk Factors and Risk Groups	Combination with chemotherapeutic agents is known to induce pulmonary toxicity. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk. **(Azoulay E, 2001)** [9]

Preventability	Careful monitoring might help to detect potentially severe events such as ARDS early in their onset. The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function along with increased neutrophil count may be preliminary signs of ARDS. In such circumstances pegfilgrastim should be discontinued at the discretion of the physician and the appropriate treatment given.
Impact on the Risk-Benefit Balance of the Product	The risk associated with the use of pegfilgrastim is minimized through provision of relevant product information to support safe use of the product
Public Health Impact	As the incidence of acute respiratory distress syndrome related to pegfilgrastim seems to be low, the public health impact of this safety concern is considered to be low despite its potentially severe clinical course

Table 12. SVII.4 - Important Identified Risk: Sickle cell crisis in patients with sickle cell disease

Potential Mechanisms	Treatment with pegfilgrastim and other colony-stimulating factors has been reported to promote erythrocyte sickling and precipitate sickle cell crisis in patients with sickle cell disease. It has been postulated that the sudden elevation in granulocytes, neutrophil activation, and cytokine release along with possible increased leukocyte adhesion may lead to a cascade of events causing vaso-occlusion in patients with sickle cell disease **(Kasi PM, 2013).** [10]
Evidence Source(s) and Strength of Evidence	Based on the published literature data and in line with the RMP for the reference product, this safety concern has been classified as an important identified risk
Characterisation of the Risk	Frequency in Viatris's (ex-MAH) clinical trials: No events of sickle cell crisis were reported from the clinical trials with Vivlipeg®. Frequency with reference product: The SmPC of the reference product lists sickle cell crisis as an uncommon undesirable effect, indicating it was identified through post-marketing surveillance but not observed in randomised, controlled clinical trials in adults and that the frequency category was estimated from a statistical calculation based upon 1,576 patients receiving Neulasta® in clinical trials. Background incidence/prevalence: Heterozygous sickle cell trait is present in up to 8% of African Americans in the United States and up to 25% in some African populations. Homozygous sickle cell disease is much less common. In Europe, sickle cell trait and sickle cell disease are very rare, with less than 1300 births estimated to be affected annually **(Rees DC, 2010)** [11]**.** Recurrent sickle-cell crises are an inherent feature of the disease; their frequency and nature

	depend on the age of the patient. Triggers of sickle-cell crisis include certain infections, high altitude, or stress; in many cases, a specific trigger cannot be identified. **(Kasi PM, 2013)** [10] Seriousness/outcomes: The published reports of sickle cell crises putatively triggered by (unpegylated) granulocyte colony stimulating factor have in most cases responded to supportive care, but fatal outcome has also been reported. **(Kasi PM, 2013)** [10] Severity and nature of risk: The majority of published reports of sickle cell crises putatively triggered by (unpegylated) granulocyte colony stimulating factor were pain crises. Vaso-occlusive crises and disseminated intravascular coagulation have also been reported. Whereas administration of granulocyte colony stimulating factor has been associated with an increased symptom score in people with heterozygous sickle cell trait, clinically severe conditions have been reported only from individuals with homozygous sickle cell disease. **(Kasi PM, 2013)** [10] Impact on individual patient: Regardless of the trigger, the clinical course of a sickle cell crisis may vary from a mild and self-limited episode to a life-threatening condition. Post-marketing data: Cumulatively up to the DLP of this RMP, the company has not received any cases for pegfilgrastim reporting events pertaining to MedDRA HLT 'Sickle cell trait and disorders' and/or SMQ 'Embolic and thrombotic events' in patients with sickle cell disease.
Risk Factors and Risk Groups	This risk is confined to individuals with heterozygous sickle cell trait or homozygous sickle cell disease. Factors such as infections, dehydration, low oxygen tension, acidosis, extreme physical exercise, physical or psychologic stress, alcohol, pregnancy, cold weather, and concomitant medical conditions (e.g. sarcoidosis, diabetes mellitus, herpes) have been identified as the cause of sickle cell crisis**. (Yale SH, 2000)** [12]
Preventability	The potential precipitation of a sickle cell crisis cannot be predicted on an individual patient level. Close monitoring of patients with sickle cell trait or sickle cell disease during treatment with pegfilgrastim and awareness of the possible association of this medicine with splenic enlargement and vaso-occlusive crisis is however a suitable measure for early detection and initiation of remedial action.
Impact on the Risk-Benefit Balance of the Product	The risk associated with the use of pegfilgrastim is minimized through provision of relevant product information to support safe use of the product

Public Health Impact	As sickle cell trait and sickle cell disease are very rare in the target population and precipitation of crises seem to be uncommon, the public health impact of this safety concern is concluded to be low

Table 13. SVII.5 - Important Identified Risk: Glomerulonephritis

Potential Mechanisms	G-CSF not only activates neutrophils but can also injure endothelial cells, modulate cytokine release and can potentially result in vasculitis. G-CSF receptors are present on myeloid lineage cells as well as on subsets of monocytes, lymphoid cells, platelets and vascular endothelial cells. G-CSF stimulation leads to mobilization of cells from the bone marrow microenvironment by release of metalloproteinases that cause shedding of adhesion molecules such as l-selectin, E-selectin and ICAM-1. G-CSF also induces E-selectin expression on endothelial cells and E-selectin ligand expression on mobilized, circulating leukocytes. This has been postulated to lead to enhanced leukocyte-endothelial cell interactions and associated vascular complications. This could result in glomerular and or renal tubular injury. Alternatively, hypersensitivity reaction to pegfilgrastim could also result in acute kidney injury (AKI). **(Arora S, 2012)** [13]
Evidence Source(s) and Strength of Evidence	Based on the published literature data and in line with the RMP for the reference product, this safety concern has been classified as an important identified risk
Characterisation of the Risk	Frequency in Viatris's (ex-MAH) clinical trials: No events of glomerulonephritis were reported from the clinical trials with Vivlipeg®. Frequency with reference product: The SmPC of the reference product lists glomerulonephritis as an uncommon undesirable effect, indicating it was identified through post-marketing surveillance but not observed in randomised, controlled clinical trials in adults and that the frequency category was estimated from a statistical calculation based upon 1,576 patients receiving Neulasta® in clinical trials. Background incidence/prevalence: Glomerulonephritis represents 10-15% of glomerular diseases. Variable incidence has been reported, in part because of the subclinical nature of the disease in more than half the affected population. Worldwide incidence of glomerulonephritis vary between 0.2/100 000/year and 2.5/100 000/year. **(McGrogan A, 2011)** [14] Seriousness/outcomes: Pegfilgrastim may cause glomerulonephritis that can be severe enough to cause AKI requiring dialysis; however, the course is usually self-limited. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of pegfilgrastim. Severity and nature of risk:

	Glomerulonephritis associated with pegfilgrastim is reversible and generally, events of glomerulonephritis are resolved after dose reduction or withdrawal pegfilgrastim. Impact on individual patient: Impact will depend on the severity of glomerulonephritis in the individual patient. Post-marketing data: Cumulatively up to the DLP of this RMP, one case has been documented for this safety concern based on the post-marketing data sources. The serious case originated from literature **(Elabd H, 2018)** [15], which reported on an elderly patient with stage IV extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. The patient developed acute kidney injury and focal necrotising and diffuse necrotising crescentic glomerulonephritis following three cycles of rituximab and bendamustine with an unspecified pegfilgrastim product. The co-administered antineoplastic agents confounded causality. The patient's elderly age might have contributed to the event occurrence in this case as well.
Risk Factors and Risk Groups	No risk groups or risk factors specific to pegfilgrastim are known. According to the SmPC of the reference product, dosing adjustment is not recommended in patients with renal impairment, including those with end stage renal disease. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim.
Preventability	Urinalysis monitoring is recommended
Impact on the Risk-Benefit Balance of the Product	The risk associated with the use of pegfilgrastim is minimized through provision of relevant product information to support safe use of the product
Public Health Impact	As clinically serious events seem to be very rare, the public health impact of this safety concern is considered to be low

Table 14. SVII.6 - Important Potential Risk: Cytokine release syndrome

Potential Mechanisms	Cytokine release syndrome (CRS) is characterized by hypersecretion of pro-inflammatory cytokines, including interleukins (IL) IL-6, IL-1, IL-5, IL-10, interferon gamma (IFN-γ), tumour necrosis factor (TNF), and TGFs by B and T lymphocytes and natural killer (NK) cells. The CRS may be further enhanced by numerous cellular interactions with bystander cells, such as endothelial cells, monocyte/macrophages, and dendritic cells, further increasing cytokine hypersecretion, aggravating symptoms, and inducing various grades of organ damage **(Cosenza M, 2021)** [16]. Studies with healthy volunteers in experimental settings have yielded variable results as to whether G-CSF may induce the release of cytokines **(Pollmacher T, 1996)** [17]**, (Pajkrt D, 1997)** [18] **& (Xu S, 2000)** [19]. Due to the association of this condition with anticancer treatments, confounding by indication cannot be excluded.

Evidence Source(s) and Strength of Evidence	Based on the published literature data and in line with the RMP for the reference product, this safety concern has been classified as an important potential risk
Characterisation of the Risk	Frequency in Viatris's (ex-MAH) clinical trials: Cytokine release syndrome was not reported as an adverse event from the clinical trials with Vivlipeg®. Frequency with reference product: The SmPC of the reference product does not list this disorder as an undesirable effect. No published case reports of cytokine release syndrome in association with a G-CSF product were identified. The Unites States Adverse Event Reporting System (AERS) database contains isolated safety reports associated with filgrastim or pegfilgrastim. Background incidence/prevalence: Cytokine release syndrome is generally attributed to treatment with certain cancer medicines. Therefore, an increased background incidence in the target population can be assumed. Seriousness/outcomes: Cytokine release syndrome is a potentially life-threatening condition, although the clinical course appears to be non-serious in the majority of patients **(Shimabukuro-VA, 2018)** [20] **& (Lee DW, 2014)** [21] Severity and nature of risk: Cytokine release syndrome (CRS) is characterised by a constellation of inflammatory symptoms following administration of natural and bispecific antibodies and, more recently, adoptive T-cell therapies for cancer. CRS can present with a variety of symptoms ranging from mild symptoms to life-threatening toxicities **(Shimabukuro-VA, 2018)** [20] **& (Lee DW, 2014)** [21] Impact on individual patient: Impact will depend on the severity and clinical course in the individual patient. Post-marketing data: Cumulatively up to the DLP of this RMP, the company has not received any cases for pegfilgrastim reporting events pertaining to MedDRA PTs 'Cytokine release syndrome', 'Cytokine storm', 'Cytokine increased'.
Risk Factors and Risk Groups	According to some published data, conditions such as stress, obesity, diabetes, and hypertension exacerbate inflammation and may constitute risk factors for CRS **(Xing X, 2023)** [22]
Preventability	No predictive or preventative measures are known

Impact on the Risk-Benefit Balance of the Product	The risk associated with the use of pegfilgrastim is minimized through provision of relevant product information to support safe use of the product.
Public Health Impact	In light of the apparently low frequency of clinically serious cases of cytokine release syndrome in association with G-CSF, the potential public health impact of this safety concern is considered to be low.

SVII.3.2. Presentation of the Missing Information

Not applicable

Part II: Module SVIII - Summary of the Safety Concerns

Table 15. SVIII - Summary of safety concerns

Important Identified Risks	• Capillary leak syndrome • Acute respiratory distress syndrome • Sickle cell crisis in patients with sickle cell disease • Glomerulonephritis
Important Potential Risks	• Cytokine release syndrome
Missing Information	• None

PART III: Pharmacoviligance Plan (including post-authorisation safety studies)

The Pharmacovigilance System Master File contains details of the system and processes that the MAH/Applicant has in place to identify and/or characterize the risks recognised in the safety specification.

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities only. The Marketing Authorization Holder has in place a routine pharmacovigilance system that will ensure compliance with regulatory agencies for pharmacovigilance responsibilities and will be sufficient to address and monitor the safety profile of pegfilgrastim. Routine practices are in accordance with standards set by health authorities and the procedures are written to meet the expectations of the health authority.

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

Specific adverse reaction follow-up questionnaires for:

- Capillary leak syndrome
- Cytokine release syndrome

to further characterise the events in the post-marketing setting.

Other forms of routine pharmacovigilance activities for safety concerns:

Not Applicable

The forms are provided in **Annex 4** - Specific Adverse Drug Reaction Follow-up Forms of the RMP.

III.2 Additional Pharmacovigilance Activities

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable, as routine pharmacovigilance only is proposed and there are no studies or other additional activities from the pharmacovigilance plan, whether ongoing, planned or completed.

PART IV: Plans for post-authorisation efficacy studies

Primary prophylaxis with granulocyte colony-stimulating factors has been shown to reduce the incidence and duration of neutropenia, febrile neutropenia, infections, hospitalisation and antibiotic use. Pegfilgrastim is at least as effective as filgrastim in the prophylaxis of chemotherapy-induced neutropenia and has improved pharmacokinetics requiring reduced administration. Relevant guidelines recommend the use of granulocyte colony-stimulating factors including pegfilgrastim to prevent febrile neutropenia and related complications where indicated**. (Abdel-Dayem HM, 1999)** [23] **& (Dagdas S, 2006)** [24]

The reference product has proven to be efficacious in numerous clinical trials in the context of various cancers, chemotherapy protocols and demographic populations. These clinical trials are complemented by extensive experience in the post-marketing setting. The efficacy of Vivlipeg® has been shown to be comparable to the reference product in an adequately designed and conducted clinical trial programme.

There is no evidence of variability of efficacy of the reference product or Vivlipeg® in certain subpopulations and there are no gaps in knowledge about efficacy in the target populations that would justify further efficacy studies within the target populations.

Therefore, no post-authorisation efficacy studies are proposed, have been imposed, or are specific obligations.

PART V: Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)

The safety information in the proposed product information is aligned to the reference biologics (Neulasta®, Amgen Europe B.V.).

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 16. Part V.1 - Description of routine risk minimisation measures by safety concern

Safety Concern	Routine Risk Minimisation Activities
Capillary leak syndrome	Routine risk communication: SmPC sections: 4.2, 4.4 and 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: In Section 4.4, warning that capillary has been reported after granulocyte-colony stimulating factor administration, description of the key symptoms of this disorder and recommendation to closely monitor and treat affected patients if symptoms develop. Other risk minimisation measures beyond the Product Information: Follow-Up form (Annex 4) Medicine's legal status: Prescription-only medicine. Restricted medical prescription: The SmPC advises in Section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.
Acute respiratory distress syndrome	Routine risk communication: SmPC sections: 4.2, 4.4. and 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: In Section 4.4, warning that pulmonary adverse reactions, in particular interstitial pneumonia, have been reported and that patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk. Other risk minimisation measures beyond the Product Information: None Medicine's legal status: Prescription only medicine. Restricted medical prescription: The SmPC advises in Section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.

Sickle cell crisis in patients with sickle cell disease	Routine risk communication: SmPC sections: 4.2, 4.4. and 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: In Section 4.4, warning that sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell trait or sickle cell disease and advice for caution (to be attentive to the possible association of this medicine with splenic enlargement and vaso-occlusive crisis) and appropriate monitoring when prescribing the product to such patients. Other risk minimisation measures beyond the Product Information: None Medicine's legal status: Prescription-only medicine. Restricted medical prescription: The SmPC advises in Section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.
Glomerulonephritis	Routine risk communication: SmPC sections: 4.2, 4.4. and 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: In Section 4.4, warning on glomerulonephritis reported with pegfilgrastim use and recommendation for urinalysis monitoring. Other risk minimisation measures beyond the Product Information: None. Medicine's legal status: Prescription-only medicine. Restricted medical prescription: The SmPC advises in Section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.
Cytokine release syndrome	Routine risk communication: SmPC section: 4.2. No further text in SmPC. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the Product Information: Follow-Up form (Annex 4). Medicine's legal status: Prescription only medicine.

	Restricted medical prescription: The SmPC advises in Section 4.2 that therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary *Table of Pharmacovigilance and Risk Minimisation Activities by Safety Concern*

Table 17. Part V.3 - Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Capillary leak syndrome	Routine risk minimization measures SmPC sections: 4.2, 4.4 and 4.8. Additional risk minimisation measures None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up questionnaire for capillary leak syndrome (**Annex 4**) **Additional pharmacovigilance activities:** None
Acute respiratory distress syndrome	Routine risk minimization measures SmPC sections: 4.2, 4.4 and 4.8. Additional risk minimisation measures None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Sickle cell crisis in patients with sickle cell disease	Routine risk minimization measures SmPC sections: 4.2, 4.4 and 4.8. Additional risk minimisation measures None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None

Glomerulonephritis	Routine risk minimization measures SmPC sections 4.2, 4.4 and 4.8. Additional risk minimisation measures None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None
Cytokine release syndrome	Routine risk minimization measures SmPC section 4.2. Additional risk minimisation measures None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up questionnaire for cytokine release syndrome (**Annex 4**). **Additional pharmacovigilance activities:** None

PART VI: Summary of the risk management plan

Summary of Risk Management Plan for Vivlipeg® (pegfilgrastim)

This is a summary of the risk management plan (RMP) for Vivlipeg® . The RMP details important risks of pegfilgrastim, how these risks can be minimised, and how more information will be obtained about Pegfilgrastim's risks and uncertainties (missing information).

Vivlipeg® 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how it should be used.

This summary of the RMP for Vivlipeg® should be read in the context of all the information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Vivlipeg®'s RMP.

I. The medicine and what it is used for

Vivlipeg® is authorised for reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes). It contains pegfilgrastim as the active substance, and it is given by pre-filled syringes, each containing 6 mg of pegfilgrastim in 0.6 ml solution for injection. The concentration is 10 mg/ml based on protein only. The concentration is 20 mg/ml if the PEG moiety is included.

Further information about the evaluation of Vivlipeg®'s benefits can be found in Vivlipeg®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/vivlipeg

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Vivlipeg®, together with measures to minimise such risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimises its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Vivlipeg® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered to patients. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Vivlipeg® . Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine/use in special patient populations etc.).

Table 18. Part VI.1 - Summary of safety concerns

List of Important Risks and Missing Information	
Important Identified Risks	• Capillary leak syndrome • Acute respiratory distress syndrome • Sickle cell crisis in patients with sickle cell disease • Glomerulonephritis
Important Potential Risks	• Cytokine release syndrome
Missing Information	• None

II. B. Summary of Important Risks

Table 19. Part VI.2 - Important Identified Risk: Capillary leak syndrome

Evidence for Linking the Risk to the Medicine	Based on the published literature data and in line with the RMP for reference biologics, this safety concern has been classified as an important identified risk
Risk Factors and Risk Groups	The cases of capillary leak syndrome reported in association with reference biologics have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis. **(MHRA, 2014)** [6]
Risk Minimisation Measures	Routine risk minimization measures SmPC sections: 4.2, 4.4 and 4.8. Specific follow-up questionnaire for capillary leak syndrome (Annex 4) Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern.
Additional Pharmacovigilance activities	None

Table 20. Part VI.3 - Important Identified Risk: Acute respiratory distress syndrome

Evidence for Linking the Risk to the Medicine	Based on the published literature data and in line with the RMP for the reference biologics, this safety concern has been classified as an important identified risk
Risk Factors and Risk Groups	Combination with chemotherapeutic agents known to induce pulmonary toxicity. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk **(Azoulay E, 2001)** [9]
Risk Minimisation Measures	Routine risk minimization measures SmPC sections: 4.2, 4.4 and 4.8. Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern
Additional Pharmacovigilance activities	None

Table 21. Part VI.4 - Important Identified Risk: Sickle cell crisis in patients with sickle cell disease

Evidence for Linking the Risk to the Medicine	Based on the published literature data and in line with the RMP for reference biologics, this safety concern has been classified as an important identified risk
Risk Factors and Risk Groups	This risk is confined to individuals with heterozygous sickle cell trait or homozygous sickle cell disease. Factors such as infections, dehydration, low oxygen tension, acidosis, extreme physical exercise, physical or psychologic stress, alcohol, pregnancy, cold weather, and concomitant medical conditions (e.g., sarcoidosis, diabetes mellitus, herpes) have been identified as the cause of the sickle cell crisis. **(Yale SH, 2000)** [12]
Risk Minimisation Measures	Routine risk minimization measures SmPC sections: 4.2, 4.4 and 4.8. Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern.
Additional Pharmacovigilance activities	None

Table 22. Part VI.5 - Important Identified Risk: Glomerulonephritis

Evidence for Linking the Risk to the Medicine	Based on the published literature data and in line with the RMP for reference biologics, this safety concern has been classified as an important identified risk
Risk Factors and Risk Groups	No risk groups or risk factors specific to pegfilgrastim are known. According to the SmPC of the reference biologics, dosing adjustment is not recommended in patients with renal impairment, including those with end-stage renal disease. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim.
Risk Minimisation Measures	Routine risk minimization measures SmPC sections 4.2, 4.4, and 4.8. Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern
Additional Pharmacovigilance activities	None

Table 23. Part VI.6 - Important Potential Risk: Cytokine release syndrome

Evidence for Linking the Risk to the Medicine	Based on the published literature data and in line with the RMP for the reference biologics, this safety concern has been classified as an important potential risk
Risk Factors and Risk Groups	According to some published data, conditions such as stress, obesity, diabetes, and hypertension exacerbate inflammation and may constitute risk factors for CRS. **(Xing X, 2023)** [22]
Risk Minimisation Measures	Routine risk minimization measures SmPC section 4.2. Specific follow-up questionnaire for cytokine release syndrome (Annex 4) Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern
Additional Pharmacovigilance activities	None

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Vivlipeg®.

II.C.2. Other studies in post-authorisation development plan

There are no studies required for Vivlipeg®.

PART VII: ANNEXES

List of Annexes

Annex 4 - Specific adverse event follow-up forms

Annex 6 - Details of proposed additional risk minimisation measures (if applicable)

Annex 4 - Specific adverse drug reaction follow-up forms

Table of Contents

Follow-up forms

1. Targeted Follow-up Questionnaire (TFUQ) for Capillary leak syndrome
2. Targeted Follow-up Questionnaire (TFUQ) for Cytokine release syndrome

Note: The above questionnaires are utilized in conjunction with standard case follow-up procedures to obtain complete case information.

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TARGETED FOLLOW UP FORM
BBL Case No.:

You recently reported the occurrence of capillary leak syndrome in a patient. We would like to ask you to complete this questionnaire. The information you provide will help us monitor and mitigate safety concerns associated with the use of Pegfilgrastim.

Answering this questionnaire is entirely voluntary and should not take more than 10 minutes of your time. Please complete the form and send it back to:

drugsafety@biocon.com

or

fax no: +91 80 6775 5323

Patients Details:

Patient's Initials	
Age/Date of birth	years/months/ (DD-MMM-YYYY)
Gender	☐ Male ☐ Female
Is the patient pregnant?	☐ Yes If yes, how many weeks: Date of LMP (Last Menstrual Period): (DD-MMM-YYYY) ☐ No
Weight	lb/kg
Height	in/cm

Product Details:

Tradename	
Strength	
Batch number	
Expiry date	
Route of administration	
Dose	
Dose frequency	
Start date	
Stop date	
Onset date for event	

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TARGETED FOLLOW UP FORM
BBL Case No.:

a) **Details of relevant concomitant medical conditions and/or therapies:**

☐ Advanced malignant diseases ☐ Sepsis

☐ Multiple chemotherapy medications ☐ Other

☐ Undergoing apheresis

☐ Concomitant or previous exposure to other biological medicinal product (including G-CSF)

Please specify (also if 'Other'):

_____

_____

_____

b) **Was treatment provided?**

☐ Yes ☐ No

If 'Yes', please describe treatment provided:

_____

_____

_____

_____

_____

<u>Outcome of capillary leak syndrome</u>:

☐ Recovered/Resolved ☐ Not recovered/resolved

☐ Recovering/Resolving ☐ Fatal

☐ Unknown ☐ Other

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TARGETED FOLLOW UP FORM
BBL Case No.:

If 'Other', please specify:

_____

_____

_____

Description of any other adverse event(s) associated with capillary leak syndrome:

_____

_____

_____

_____

_____

_____

_____

Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign:

Occupation: Date:

`

TARGETED FOLLOW UP FORM
BBL Case No.:

Biocon Biologics is committed to holding patient's and reporter's personal data in strict confidence. Personal data, here, means any information by which a person is, directly or indirectly, identified or identifiable, which includes, but is not limited, to name, address, contact number, email address, genetic data and data concerning health. Biocon Biologics strictly adheres to applicable data privacy and data integrity laws, including, but not limited to, General Data Protection Regulations [EU] 2016/679 ["GDPR"] or its equivalent, as amended from time to time.

Additional Information:

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TARGETED FOLLOW UP FORM
BBL Case No.:

You recently reported the occurrence of cytokine release syndrome in a patient. We would like to ask you to complete this questionnaire. The information you provide will help us monitor and mitigate safety concerns associated with the use of Pegfilgrastim.

Answering this questionnaire is entirely voluntary and should not take more than 10 minutes of your time. Please complete the form and send it back to:

drugsafety@biocon.com

or

fax no: +91 80 6775 5323

Patients Details:

Patient's Initials	
Age/Date of birth	years/months/ (DD-MMM-YYYY)
Gender	☐ Male ☐ Female
Is the patient pregnant?	☐ Yes If yes, how many weeks: Date of LMP (Last Menstrual Period): (DD-MMM-YYYY) ☐ No
Weight	lb/kg
Height	in/cm

Product Details:

Tradename	
Strength	
Batch number	
Expiry date	
Route of administration	
Dose	
Dose frequency	
Start date	
Stop date	
Onset date for event	

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TARGETED FOLLOW UP FORM
BBL Case No.:

Outcome of cytokine release syndrome:

☐ Recovered/Resolved ☐ Not recovered/resolved

☐ Recovering/Resolving ☐ Other

☐ Unknown

If 'Other', please specify:

_____

_____

_____

a) Was treatment provided/ urgent medical attention required?

☐ Yes ☐ No

If YES, please treatment/urgent medical attention provided:

_____

_____

_____

_____

_____

_____

b) Any associated symptoms/adverse reactions reported?

☐ Fever ☐ Neurologic toxicity

☐ Malaise ☐ Acute Respiratory Distress Syndrome

☐ Nausea ☐ Renal failure

☐ Headache ☐ Hepatic failure

☐ Myalgia ☐ Disseminated intravascular coagulation

☐ Tachycardia ☐ Other

☐ Hypotension

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TARGETED FOLLOW UP FORM
BBL Case No.:

If 'Other', please specify:

_____

_____

_____

_____

_____

c) **Details of relevant concomitant therapies:**

☐ Concomitant or previous exposure to other biological medicinal product (including G-CSF)

Please specify:

_____

_____

_____

_____

_____

Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign:

Occupation: Date:

TARGETED FOLLOW UP FORM
BBL Case No.:

Biocon Biologics is committed to holding patient's and reporter's personal data in strict confidence. Personal data, here, means any information by which a person is, directly or indirectly, identified or identifiable, which includes, but is not limited, to name, address, contact number, email address, genetic data and data concerning health. Biocon Biologics strictly adheres to applicable data privacy and data integrity laws, including, but not limited to, General Data Protection Regulations [EU] 2016/679 ["GDPR"] or its equivalent, as amended from time to time.

Additional Information:

Annex 6 - Details of proposed additional risk minimisation measures (if applicable)

Not applicable